

* Application No. 09/944,852
Amendment Dated 10/7/03
Reply to Office Action mailed 8/12/03

Listing of the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application.

Claims 1-22 (cancelled)

Claim 23 (previously presented): The antibody of Claim 27 which is a monoclonal antibody.

Claim 24 (previously presented): The antibody of Claim 27 which is a humanized antibody.

Claim 25 (previously presented): The antibody of Claim 27 which is an antibody fragment.

Claim 26 (currently amended): The antibody of Claim 27 which is a labeled.

Claim 27 (currently amended): An antibody that specifically binds to the polypeptide shown in Figure 32 (SEQ ID NO:83).

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REMARKS

Claims 23-27 are pending in this application. Applicants have cancelled claim 22 without prejudice or disclaimer. Claim 26 has been amended to remove the article "a," which inadvertently appeared for the first time, as the Examiner kindly notes, before the word "labeled" in the response filed 12 May 2003. Claim 27 has been amended to clarify that "binds" has its ordinary meaning to one of skill in the art.

Applicants respectfully request that the Examiner consider the following remarks in response to the Office Action.

Rejection of Claims Under 35 U.S.C. §112, Second Paragraph- Indefiniteness

The Examiner rejected claims 22 and 27 as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner contends that it is unclear what Applicant means by the recitation of "binds" in claim 22 and "specifically binds" in claim 27. Applicants have cancelled claim 22 and amended claim 27 to clarify that "binds" in claim 27 has its ordinary meaning to one of skill in the art. Applicants submit that they have overcome the Examiner's rejection of claim 27 and respectfully request that it be withdrawn.

Rejection of Claims Under 35 U.S.C. § 112, First Paragraph - Enablement

The Examiner has rejected claims 22-27 as failing to comply with the enablement requirement. More specifically, the Examiner alleges that the function of PRO361 is unknown and therefore one of ordinary skill in the art would have to engage in an inordinate amount of work and experimentation to find out not only the identity of what the antibodies of PRO361 are useful for, but also the use of PRO361 itself.

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Applicants respectfully disagree that the function of PRO361 is unknown. More specifically, Example 34, found on page 141 of the application, describes a Mixed Lymphocyte Reaction Assay ("MLR") in which PRO361 tested positive, demonstrating that PRO361 functions as an inhibitor of the proliferation of stimulated T-lymphocytes.

MLR is a well-established *in vitro* assay for assessing the ability of a test compound to stimulate or suppress T cell proliferation, and consequently the immune response of an individual. In brief, in a MLR assay, an immune response is produced by mixing T cells from antigenically distinct individuals and allowing them to react with one another in cell culture. The MLR assay is described in standard textbooks, including, for example, *Current Protocols in Immunology*, unit 3.12; edited by J.E. Coligan, A.M. Kruisbeek, D.H. Marglies, E.M. Shevach, W. Strober, National Institutes of Health, published by John Wiley & Sons, Inc., which is referenced in Example 34 on page 141 of the specification. The entire content of the *Current Protocols in Immunology* reference is expressly incorporated by reference into the disclosure of the present application.

MLR has been extensively used and is considered to be the best *in vitro* model available to study graft-versus-host disease and graft rejection. It is well known that the transplantation of tissues or organs between individuals with MHC incompatibilities quickly activates the recipient's immune system which then attempts to destroy the transplanted tissue or organ. Transplantation across minor histocompatibility loci generally induces a more indolent response. Physicians analyze the major and minor histocompatibility differences to predict the success of the graft and to adjust the aggressiveness of immunosuppressive therapy. MLR can be monitored qualitatively, for example, by following the incorporation of tritiated thymidine during DNA synthesis, by observing blast formation or by similar methods known in the art.

Inhibitors of MLR find utility in suppressing unwanted immune responses, which might, for example, result in graft rejection. For example, the ability of tepoalbin, an immunomodulatory compound, to suppress graft-versus-host reaction, has been demonstrated in a MLR assay (Fung-Leung *et al.*, *Transplantation* 60:362-8 (1995))

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(See Appendix A). Other immunosuppressants have also been routinely identified by MLR.

For example, the specification, on page 141, discusses the inhibitory activity of PRO361 (with regard to T cell proliferation), as demonstrated in a MLR assay. At lines 8-9 of page 141, the specification sets forth how PRO361 may be used, based on its function: “[c]ompounds which inhibit proliferation of lymphocytes are useful therapeutically where suppression of an immune response is beneficial.” Accordingly, PRO361 polypeptides or their agonists are useful candidates for suppressing harmful immune response, e.g., in the case of graft rejection or graft-versus-host disease. Similarly, inhibitors (antagonists) of PRO361 find utility in stimulating T cell response, e.g. in the case of leukemia, and other types of cancer, and in immunocompromised patients, such as AIDS sufferers.

Therefore, one of skill in the art would know that antibodies to PRO361, wherein PRO361 is acting as an agonist, are useful for suppression of an immune response. Alternatively, an antibody to PRO361, wherein PRO361 is acting as an antagonist or inhibitor, would find utility in stimulating a T cell response. Thus, Applicants maintain that the application is enabled and that undue experimentation is not required to practice the claimed invention.

Further, for the additional reasons stated in the response of 12 May 2003 to the Office Action of February 11, 2003, Applicants submit that the present application is enabled.

Specifically, the Federal Circuit has stated that:

[t]he determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art (citations omitted). The test is not merely quantitative, since a *considerable amount of experimentation is permissible*, if it is merely routine, or *if the specification provides a reasonable*

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amount of guidance with respect to the direction in which the experimentation should proceed. See *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

The Federal Circuit has also set forth several factors to consider when determining whether the experimentation required to practice an invention is undue: (1) the nature of the invention, (2) the state of the prior art, (3) the relative skill of those in the art, (4) the level of predictability in the art, (5) the existence of working examples, (6) the breadth of the claims, (7) the amount of direction or guidance by the inventor, and (8) the quantity of experimentation needed to make or use the invention. *Id.* An analysis of these factors further illustrates that undue experimentation is not required to practice the claimed invention.

First, the claimed invention is an antibody, including monoclonal antibodies, humanized antibodies, antibody fragments and labeled antibodies, that binds to the polypeptide shown in Figure 32 (SEQ ID NO: 38).

Second, as summarized in the abstract of the review article entitled, "The Genetic Engineering of Monoclonal Antibodies," which appeared in the February 1994 issue of the *Journal of Immunological Methods* (Appendix B), and as the PTO recognizes, the state of the prior art in antibody technologies is such that methods for preparing antibodies that bind to a particular polypeptide were well-known at the time the application was filed. See Owens et al., The Genetic Engineering of Monoclonal Antibodies, *Journal of Immunological Methods*. 1994 Feb 10;168(2):149-65 (Appendix B). See also *Synopsis of Application of Written Description Guidelines* at 59-60 (<http://www.uspto.gov/web/menu/written.pdf>) (attached hereto as Appendix C).

Third, as the PTO also recognizes, the level of skill in the mature art of antibodies is high and advanced. See *Synopsis of Application of Written Description Guidelines* at 59-60 (<http://www.uspto.gov/web/menu/written.pdf>) (Appendix C). See also Owens et al., The Genetic Engineering of Monoclonal Antibodies, *Journal of Immunological Methods*. 1994 Feb 10;168(2):149-65 (Appendix B).

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Fourth, given the well-known methods for preparing antibodies, although routine experimentation may be required, the art is predictable.

Fifth, from pages 81-89 of the specification, Applicants describe various uses for the claimed antibodies, as well as methods for producing polyclonal, monoclonal, human, humanized, bispecific, and heteroconjugate antibodies. Further, at page 141, Example 34 of the specification, Applicants describe a MLR assay which demonstrated that the function of PRO361, the protein bound by the claimed antibody, is to inhibit the proliferation of stimulated T-lymphocytes.

Sixth, the claims are not overly broad, but rather are directed only to antibodies that bind PRO361.

Seventh, as discussed above, at pages 81-89 of the specification, Applicants have disclosed how to make and use the various types of claimed antibodies. In addition, at page 141 of the specification, Applicants have disclosed the function of PRO361, which is bound by the claimed antibodies.

Finally, eighth, because of the state of the art, the level of skill in the art and the significant disclosure found in the specification, any experimentation that might be required to practice the claimed invention would be routine and not undue. Therefore, Applicants submit that the present invention is enabled by the specification and respectfully request that the Examiner withdraw this ground of rejection.

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CONCLUSION

Applicants believe this Amendment and Request for Reconsideration fully responds to the Office Action. Applicants respectfully request the Examiner grant allowance of this application. The Examiner is invited to contact the undersigned attorney for the Applicant via telephone if such communication would expedite this application.

Applicants believe no fee is due in connection with the filing of this Reply, however, should any fees be deemed necessary for any reason relating to this paper, the Commissioner is hereby authorized to deduct said fees from Brinks Hofer Gilson & Lione Deposit Account No. 23-1925. A duplicate copy of this document is enclosed.

Respectfully submitted,

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